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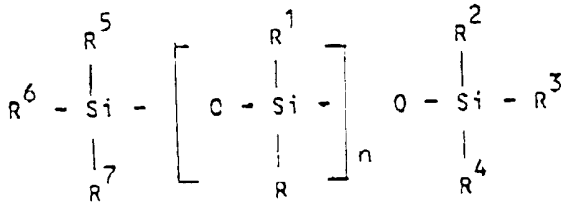
## (54) Therapeutic opthalmic compositions containing silicone polymer fluids and a process for preparing same.

(57) A composition comprising an ophthalmic drug and a polysiloxane of the formula I



in which the organic moieties, R, R', $R^2$, $R^3$, $R^4$, $R^5$, $R^6$, $R^7$, are selected from the group consisting of alkyl, and aralkyl, and mixtures thereof; the organic moieties may be the same or different, and n is a number selected to provide a viscosity of the polysiloxane of from 3-70 centistokes.

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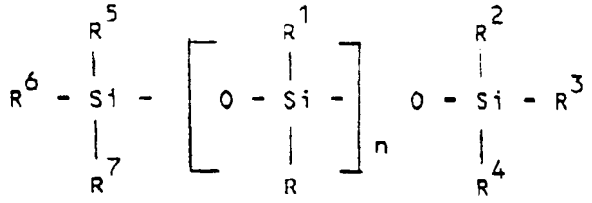
The present invention relates to novel therapeutic ophthalmic compositions containing silicone polymer fluids, and a process for preparing such ophthalmic compositions.

In order for a pharmaceutical vehicle to be useful as an ophthalmic vehicle, it is necessary that it be non-irritating to the eye, and non-toxic. In order for it to be most effective it must not blur the vision. For certain drugs, unstable in aqueous solution an oil based vehicle is required. For other drugs, which are water soluble and poorly absorbed, it is possible to promote better biovailability through the use of an oil vehicle (Biopharm. and Drug Disposit, Vol. 7 page 453, 1986). Nevertheless, known oil based ophthalmic vehicles blur the eye. Known vehicles are edible vegetable oils such as cottonseed oil, soybean oil, coconut oil, rapeseed oil, peanut oil, olive oil, palm oil, palm kernel oil, castor oil, sunflower seed oil, wall flower oil, sesame oil; or mineral oils. None of these previously known oils satisfy the 3 above mentioned criteria; all of these oils, while being non-irritating and toxic, blur the vision.

The present invention provides ophthalmic drugs, in an oil based vehicle which is non-irritating, non-toxic and yet does not blur the vision.

## DETAILED DESCRIPTION OF THE INVENTION

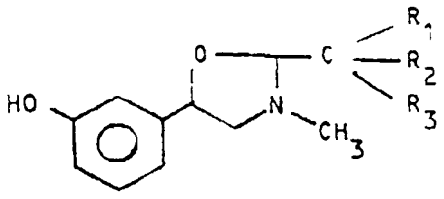
It is a discovery of the invention that silicone polymers of the formula I



in which the organic moieties, R, R′, $R^2$, $R^3$, $R^4$, $R^5$, $R^6$, $R^7$ are selected from the group consisting of alkyl, and aralkyl, and mixtures thereof; the organic moieties may be the same or different, and n is a number selected to provide a viscosity of the silicone polymer vehicle of from 3-70 centistokes, is useful as a unique ophthalmic vehicle which does not blur vision, is non-toxic and non-irritating to the eye.

The silicone polymer vehicle, at a viscosity of 3-70 centistokes may be combined with various ophthalmic drugs to provide novel ophthalmic compositions.

The silicone polymers of the above mentioned viscosity, may for example be combined with oxazolidine pro-drugs of 1-m-hydroxy--/(methylamino) methyl/ benzyl alcohol commonly known as phenylephrine, of the formula II



wherein $R_1$, $R_2$, and $R_3$ are any aliphatic combinations of $C_1$-$C_5$, and $R_1$ may also be hydrogen or the non-toxic pharmaceutically acceptable salt forms thereof; to provide a stable, ophthalmic composition.

Phenylephrine is a well-known pharmaceutically active amine whose principal use in the field of ophthalmology is as a mydriatic. There are, however, certain known disadvantages associated with the use of phenylephrine as a mydriatic agent. Those disadvantages have limited the use of this highly effective drug. Thus, in spite of the fact that it is one of the most effective mydriatics available, its use is significantly limited because of the significant side effects which may occur in some individuals treated with phenylephrine. Those unwanted significant side effects range from hypertension, syncope, and even in some cases to myocardial infarction, leading to death. Such side effects have been reported with doses of topical ocular phenylephrine.

One approach which has been used from time to time in the past is the effort to develop successful prodrugs of phenylephrine. The term prodrug refers to a therapeutic agent that requires enzymatic



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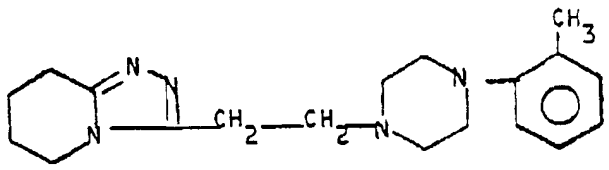
transformation to demonstrate therapeutic activity. In other words the prodrug itself is not therapeutically active, but once subjected to enzymatic activity by the host organism it is converted to an active drug. In the past there have been some attempts to make prodrugs of phenylephrine, with varying degrees of success. For example, Mindel et al., "Is Phenylephrine Pivalate a Prodrug?", Arch. Ophthalmol. 98, 2220 (1980) suggests the reaction product of phenylephrine and pivalic acid to provide a pivalic acid ester as a possible prodrug. However, as reported in that article, phenylephrine pivalate itself produces these side effects. And, it goes without saying that to have a successful prodrug, the prodrug itself must not produce the unwanted side effects, even though it may be effectively converted within the body to the active drug. Johansen et al., "Prodrugs as Drug Delivery Systems XXV: Hydrolysis of Oxazolidines--A Potential New Prodrug Type", Journal Pharm. Sci., 72, 1294 (1983) discloses some prodrug possibilities of ephedrine. However, ephedrine is not commonly used ophthalmically and is biologically different in activity than phenylephrine, with ephedrine being used orally for narcolepsy, bronchial asthma and nasal congestion. In contrast, the oxazolidine derivative of phenylephrine increases the bulk considerably on the amine function, the latter of which is responsible for phenylephrine's activity. With the addition of oxazolidine to the amine function, the prodrug would be expected to be devoid of alpha-adrenergic activity (A. Burger, "Medicinal Chemistry, 3rd ed., Wiley-Interscience, 1970, p. 1248).

Accordingly, there is a continuing and real need for safe and effective prodrugs of phenylephrine which can be safely and effectively delivered to the eye.

The prodrug of phenylephrine is not stable in aqueous solution. Thus, it is necessary that effective ophthalmic compositions include the prodrug in an oil suspension.

The composition of the invention is the only manner in which this prodrug can be delivered to the eye in a non-irritating, non-toxic manner without blurring the vision.

The silicone fluid of a viscosity of 3-70 centistokes may also for example, be combined with the mydriatic drug dapiprazole of the formula III



to provide a non-irritating, non-toxic, non-blurring ophthalmic composition.

The compounds of formula II or III themselves, or their base form or pharmaceutically acceptable non-toxic acid salts thereof can be combined with the silicone polymers of the viscosity of 3-70 centistokes. Such acid salt forms of biologically active compounds which are non-toxic are for example, those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric, and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, benzoic, glutamic and salicylic.

Such pharmaceutically accepted salts of the base form of the compounds of formula II or III previously mentioned may be synthesized by conventional, chemical methods. Generally the salts are prepared by reacting the free base form with stoichiometric amounts or with an excess thereof of the desired salt forming inorganic or organic acid, in a suitable solvent, or various combinations of solvents. For example the free base can be dissolved in a mixed aqueous solution of the appropriate acid and the salt recovered by standard techniques, such as evaporation of the solution.

Other examples of ophthalmic drugs which may be combined with the silicone polymers to provide an ophthalmic composition are: dipivefrin, proparaciane, chlorenphamicol, penicillin and penicillin derivatives, epinephrine and epinephrine salts, sodium sulfacetamide, cephalosporin derivatives, pilocarpine and its salts, echothiophate iodide, prednisolone acetate, physostigmine sulfate, and isofluorophate.

The amount of prodrug in the ophthalmic composition of the present invention can comprise from about 0.00125% by weight of the composition up to about 10% by weight of the composition which is to be topically applied to the eye. Preferably the composition is from about 0.5% by weight of the prodrug of phenylephrine (formula II) or dapiprazole (formula III) up to about 5% by weight of the prodrug or dapiprazole. The balance of the composition is primarily the silicone fluid at a viscosity of 3-70 centistokes.

The pharmaceutical composition, besides the silicone fluid may contain other non-toxic auxiliary substances such as anti-bacterials, anti-fungals, anti-oxidants, wetting agents, preservatives and the like. Examples include anti-bacterial components such as chlorobutanol, methyl and propyl paraben, and to the



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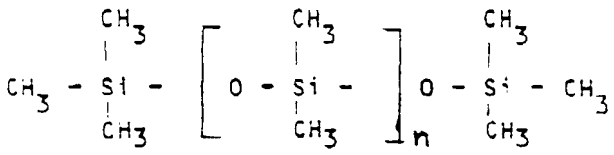
degree they are soluble quaternary ammonium compounds, phenylmercuric salts known to have cold sterilizing properties and which are non-injurious in use, and thimerosal; wetting agents such as plutonic P-103, SPAN with low HLB values (HLB below 5); antifungals such as methyl and propyl paraben; preservatives such as alpha-topoceroi and BHA; and other conventional ingredients such as sorbitan monolaurate, triethanolamine oleate, polyoxyethylene sorbitan monopalmitylate, monothioglycerol, thiosorbitol, and ethylenediamine tetracetic acid, to the degree they are soluble, and the like.

Example of silicone fluids of the formula I are polydimethylsiloxane of the formula



wherein n is selected to provide a viscosity of the polydimethylsiloxane of 3-70, and polyphenylmethylsiloxane.

A source of polydimethylsiloxane is DOW CORNING 360 MEDICAL FLUID. DOW CORNING 360 MEDICAL FLUID can be purchased at a viscosity of 3, 20, 100 centistokes, and to make polydimethylsiloxane of intermediate viscosity one appropriately dilutes one viscosity of the DOWN CORNING 360 MEDICAL FLUID with another. For examole, to obtain a viscosity of 11.5, DOW 360 with a viscosity of 3 and 20 centistokes is mixed 1:1.

Another source of polydimethylsiloxane is DOW 200 FLUID, available in viscosities from .65 - 300,000.

A source of phenylmethylsiloxane is DOW 510 FLUID. Another source of polyphenylmethylsiloxane is RHODOSIL HUILE 550 from Rhone-Poulenc.

The invention also relates to preparing the ophthalmic composition.

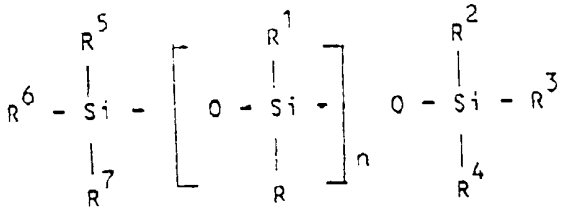
Generally, the ophthalmic drug of choice is micronized to prevent corneal abrasion. A wetting agent is added to permit interaction between the polydimethylsiloxane and the drug. About 25% of the desired amount of polydimethylsiloxane is mixed with the drug and wetting agent, and the solution is mixed, preferably in a high speed mixer. The remainder of the polydimethylsiloxane is then added. As indicated above, other auxiliary substances may be then added as desired.

An example of typical pharmaceutical composition to be used with the compound 2-t-butyl-3-methyl-5-(m-hydroxyphenyl)-1,3--oxazolidine in its base form, includes the following:

| Ingredients | Percent |
|---|---|
| 2-t-butyl-3-methyl-5-(m-hydroxyphenyl)-1,3-oxazolidine..... | 1.00 |
| Chlorobutanol..... | 0.25 |
| Wetting Agent, Arlacel-85..... | 0.05 |
| Dow 360 Medical Fluid, 3 centistokes..... | Balance |

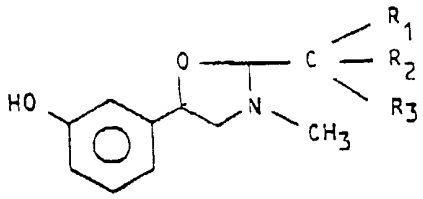
## Claims

1. A composition comprising an ophthalmic drug and a polysiloxane of the formula I



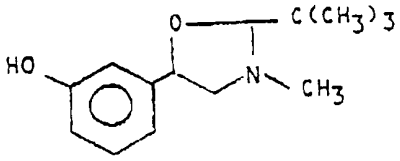
in which the organic moieties, R, R', $R^2$, $R^3$, $R^4$, $R^5$, $R^6$, $R^7$, are selected from the group consisting of alkyl, and aralkyl, and mixtures thereof; the organic moieties may be the same or different, and n is a number selected to provide a viscosity of the polysiloxane of from 3-70 centistokes.

2. An opthalmic composition as in claim 1 wherein said ophthalmic drug comprises a compound of the formula



wherein $R_1$, $R_2$, and $R_3$ are any aliphatic combinations of $C_1$-$C_5$, and $R_1$ may also be hydrogen or the non-toxic pharmaceutically acceptable salt forms thereof.

3. A composition, as in claim 2 wherein said ophthalmic drug comprises 2-t-butyl-3-methyl-5-(m-hydroxyphenyl)-1,3-oxazolidine of the formula



4. A composition, as in claim 2 further comprising one or more of anti-bacterials, antifungals, anti-oxidants, wetting agents, or preservatives.

5. A composition, as in claim 2 wherein said antibacterial comprises chlorobutanol.

6. A composition, as in claim 1 where said compound of formula I is polydimethylsiloxane.

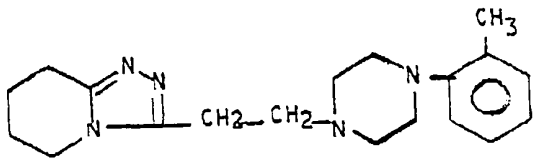
7. A composition, as in claim 1 where said compound of formula I is phenylmethylsiloxane.

8. A composition, as in claim 6 where said polydimethylsiloxane has a viscosity of 3-20 centistokes.

9. An opthalmic composition, as in claim 1 wherein the compound of formula II comprises .00125 -10% of the total composition.

10. A composition, as in claim 1 wherein the compound of formula II comprises .00125 - 2% of the total composition.

11. An ophthalmic composition as in claim 1 wherein said ophtahlmic drug comprises a compound of the formula





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dapiprazole or ts non-toxic pharmaceutically acceptable salts of a viscosity of 3-70 centistokes, and polydimethylsiloxane with a viscosity of 3-70 centistokes.

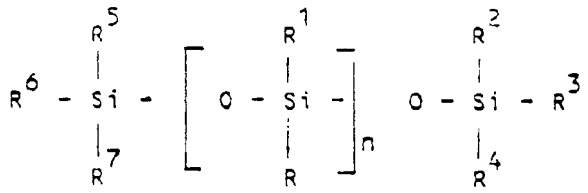
12. An ophthalmic composition, as in claim 10 further comprising one or more of anti-bacterials, antifungals, anti-oxidants, wetting agents, or preservatives.

13. An ophthalmic composition, as in claim 11 wherein said polydimethylsiloxane has a viscosity of 3 centistokes.

14. An ophthalmic composition, as in claim 11 wherein said polydimethylsiloxane has a viscosity of 20 centistokes.

15. A composition as in claim 11 wherein dapiprazole comprises .001 - 10% of the total composition.

16. A process for preparing an ophthalmic vehicle comprising mixing a poly-siloxane of the formula



in which the organic moieties, R, $R^1$, $R^2$, $R^3$, $R^4$, $R^5$, $R^6$, $R^7$, are selected from the group consisting of alkyl, and aralkyl, and mixtures thereof; the organic moieties may be the same or different, and n is a number selected to provide a viscosity of the poly-siloxane of from 3-70 centistokes; with an ophthalmically active compound.

17. A process for preparing an ophthalmic composition as in claim 16 comprising

(a) micronizing the powder of an ophthalmic drug

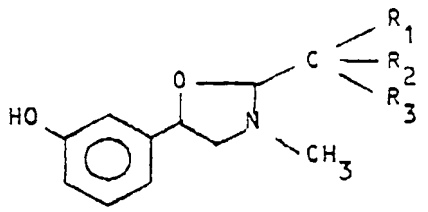
(b) adding a wetting agent to a sufficient amount of micronized compound to provide a .00125-10% of the total composition

(c) adding about 25% of the total desired polysiloxane of formula I of the viscosity between 3-70 centistokes

(d) mixing throughly

(e) adding the balance of the compound of formula I.

18. A process as in claim 17, wherein said ophthalmic drug comprises a compound of the formula



wherein $R_1$, $R_2$, and $R_3$ are any aliphatic combinations of $C_1$-$C_5$, and $R_1$ may also be hydrogen or the non-toxic pharmaceutically acceptable salt forms thereof and or dapiprazole.

19. A process, as in claim 17 further comprising one or more of anti-bacterials, antifungals, anti-oxidants, wetting agents, or preservatives.

20. A process as in claim 17 wherein the concentration of dapiprazole or compound of formula II comprises .25 - 5% of the total composition.

21. A process, as in claim 17 wherein the mixing is done in a high speed mixer.

22. A process, as in claim 17 wherein the compound of formula I is polydimethylsiloxane.

23. A process, as in claim 17 wherein the compound of formula I is phenylmethylsiloxane.

24. A composition, as in claim 1 wherein if any of $R_1$, -$R_7$ are alkyl, the alkyl group is a lower alkyl group.

25. A composition, as in claim 24 wherein the lower alkyl group comprises 1-6 carbon atoms.



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# EUROPEAN SEARCH REPORT

Application Number

EP 88 10 1032

## DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document with indication, where appropriate, of relevant passages | Relevant to claim | CLASSIFICATION OF THE APPLICATION (Int. Cl.4) |
|---|---|---|---|
| X,Y | US-A-2 727 846 (R.L. TALBOT)<br>* Column 1, lines 15-17; Claims * | 1-10,12-16,18-20,24,25 | A 61 K 9/06<br>A 61 K 47/00 |
| Y | US-A-3 880 996 (A.I. FISHER)<br>* Column 2, lines 20-68; claims * | 1-10,12,15,16,24,25 | |
| Y | CHEMICAL ABSTRACTS, vol. 104, no. 20, 19th may 1986, page 367, abstract no. 174346y, Columbus, Ohio, US; P. KUMAR et al.: "Dermal and mucosal irritancy of indigenous silicone fluids", & INDIAN J. PHARM. SCI. 1985, 47(3), 104-7<br>* Whole abstract * | 1 | |
| D,Y | JOURNAL OF PHARMACEUTICAL SCIENCES, vol. 72, no. 11, November 1983, pages 1294-1298, American Pharmaceutical Association; M. JOHANSEN et al.: "Prodrugs as drug delivery systems XXV: Hydrolysis of oxazolidines - A potential new prodrug type"<br>* Whole document * | 1-10,18 | |

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

A 61 K

The present search report has been drawn up for all claims

| Place of search | Date of completion of the search | Examiner |
|---|---|---|
| THE HAGUE | 18-03-1988 | BERTE M.J. |

CATEGORY OF CITED DOCUMENTS

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